## REMARKS

Claims 1, 5, 6, 14-15 and 17-26 are pending. Claims 18-26 are withdrawn. Claims 2-4, 7-13, 16 and 27-39 have been canceled. Claims 1, 5, 6, and 15 have been amended as described herein. The amendments add no new matter and entry of these amendments is respectfully requested.

Regarding all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

### Continued Examination

Applicants thank the Examiner for acknowledgement of Applicants' request for continued examination under 37 CFR 1.114. Action at page 2. Applicants thank the Examiner for withdrawing the finality of the previous Office Action and entering the amendments filed on May 25, 2007. *Id.*

### Declaration under 37 C.F.R. § 1.132

Applicants point out that a declaration executed November 20, 2007, accompanies this response. This is a third declaration by the Applicants' Chief Scientific Officer, Dr. Uwe D. Staerz and shall be referred to herein as Dr. Staerz's 3rd Declaration.

### Supplemental Information Disclosure Statement

Applicants note that a Supplemental IDS is filed herewith. This IDS supplies copies of references that were cited in the Declaration filed May 25, 2007, and that are not otherwise made of record.

**Rejections under 35 U.S.C. § 112, second paragraph**

Claims 1, 14, 15, 17, 33, 36, 37 and 39 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Action at page 3. Specifically, the Office asserted that these claims omit the allegedly essential step of developing a T cell activation. *Id.*

Without acquiescing in any way to the Office's contentions, Applicants have introduced the phrase "upon transplantation" to independent claim 1, from which claims 14, 15 and 17 depend directly or indirectly (while claims 33, 36, 37 and 39 have been canceled). As discussed throughout the specification , transplantation of alloantigens generally results in T cell activation and is taught in conjunction with the practice of the claimed invention. See, e.g., paragraphs 0003, 0008, 0017, 0018, or 0051 of the published application (Application Publication No. 2005/0042217).

Accordingly, Applicants respectfully submit that the currently-pending claims are free of any indefiniteness regarding a step for activating T cells and respectfully request withdrawal of these rejections.

**Rejections under 35 U.S.C. § 112, first paragraph**

Claims 1, 14, 15, 17, 33, 36, 37 and 39 also were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled. Action at page 4. Specifically, the Office asserted that these claims are not enabled by the disclosure as they omit the allegedly essential or critical step of exposing cells/tissues to an allogenic tissue which could mount an adaptive T cell response. *Id.*

As noted above, and again without acquiescing in any way to the Office's contentions, Applicants have introduced the phrase "upon transplantation" to independent claim 1, from which claims 14, 15 and 17 depend directly or indirectly (and claims 33, 36, 37 and 39 have been canceled). As recognized by the Examiner, such exposure is described throughout the specification (Action at page 4), thereby clearly providing enabling support for the now-amended claims.

Accordingly, Applicants respectfully request withdrawal of the 112, first paragraph rejections based on alleged omission of certain steps.

**Rejections under 35 U.S.C. § 112, first paragraph – *in vivo* aspects**

Claims 33-37 and 39 also were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled. Action at page 4. In sum, the Office asserted that *in vivo* aspects of these claims allegedly are not enabled by the disclosure. Action at pages 4-9.

As Applicants have canceled claims 33-37 and 39, Applicants respectfully submit that these 112, first paragraph, rejections are rendered moot. Nonetheless, Applicants wish to point out that the cancellation of these claims in no way indicates Applicants' acquiescence to the Office's contentions regarding alleged non-enablement *of in vivo* aspects of the claimed invention.

Moreover, Applicants thank the Examiner for withdrawing previous enablement rejections and for acknowledging enablement for methods of IV injection prior to transplantation. Action at pages 4-5.

**Rejections under 35 U.S.C. §102(b) – Edge reference**

The Office has reiterated the previous anticipation rejection of Claims 1, 5, 6 and 14 under 35 U.S.C. §102(b) by U.S. Patent Application No. 2002/0127205, Edge *et al.* (hereinafter "Edge"), again asserting that the claims fail to exclude the possibility of including the CD8 beta-chain in the expression vector. Action at pages 10-12. Specifically, the Office contended that the term "consisting essentially of" does not clearly exclude the beta-chain. Action at p. 11. Further, with respect to claims 14, 15 and 17, the Office asserted that Edge discloses human CD8-alpha, by reference to Shiue, *et al.* (1988) J. Exp. Med. 168(6): 1993-2005. Action at p. 10.

Without acquiescing to the Office's assertions, and solely for purposes of advancing prosecution, Applicants have amended independent claims 1, 5 and 6, as well as dependent claim 15, to recite the term "consisting of" rather than "consisting essentially of." Applicants respectfully submit that this language clearly and unmistakably excludes the beta-chain from the

expression vector. Further, dependent claims 14 and 17 are similarly amended, as claim 14 depends from amended claim 1, 5 or 6; and claim 17 depends from amended claim 15.

Accordingly, for at least the above reason, Applicants respectfully request withdrawal of the anticipation rejections based on Edge.

**Rejections under 35 U.S.C. §102(b) – Tykocinski references**

The Office also rejected claims 1, 5, 6, 14, 15 and 17 under 35 U.S.C. §102(b) as being anticipated by any one of U.S. Patent Nos. 5,623,056; 5,601,828; or 5,242,687, each to Tykocinski, *et al.* (hereinafter "the Tykocinski patents"). Action at page 13. The Office contended that Tykocinski '828, for example, teaches specific and nonspecific immunomodulation using CD8 compositions and specifically defines CD8 to be CD8 alpha. *Id.* With respect to claims 15 and 17, the Office contended that human CD8 alpha chains also are disclosed in the Tykocinski patents. Action at page 14.

Applicants respectfully traverse, as none of the Tykocinski patents teach the specific inhibition of T cells using an expression vector encoding a CD8 alpha chain that includes a transmembrane domain for expression on the cell surface. The Tykocinski patents discuss specific T cell inhibition only when using CD8:ligand constructs, rather than CD8 alpha alone. Further, the constructs are used to coat cells externally via their ligand portions, rather than insertion via a transmembrane domain of CD8. Thus, as elaborated further below and in Dr. Staerz's 3rd Declaration, the Tykocinski patents fail to teach at least these two aspects of the invention as currently claimed.

First, the Tykocinski patents fail to teach the use of CD8 alpha alone (or a functional domain thereof) to specifically inhibit T cell responses (claims 1 and 5) or to extend the survival of an allograft in a recipient (claim 6). Rather, the Tykocinski patents teach only that "a native or genetically engineered CD8 peptide can inhibit T cells and other cells *when said CD8 peptide is associated with a second ligand* that would otherwise function as a cellular activator." See, Tykocinski '828, column 3, lines 40-43; Tykocinski '056, column 3, lines 40-43; and Tykocinski '687, column 3, lines 44-48 (emphasis added). The specifications go on to describe and

exemplify various CD8:ligand conjugates, all of which involve moieties not naturally associated with CD8 that are linked to the CD8 peptide. See Dr. Staerz 3rd Declaration, at ¶¶ 5-6.

Moreover, the Tykocinski patents require at least one such secondary ligand for pharmacological activity, specifying that "[a] pharmacologically active CD8 composition comprises a CD8 peptide *associated with one or more secondary ligands* that serve to direct CD8's inhibitory ligand activity to specific target cells." See, Tykocinski '828, column 2, lines 25-28; Tykocinski '056, column 2, lines 25-28; and Tykocinski '687, column 2, lines 27-30 (emphasis added). Accordingly, the Tykocinski patents are devoid of any teaching to use CD8 alpha alone to bring about pharmacological activities, such as inhibiting T cells or extending allograft survival. Instead, the Tykocinski patents require association with one or more other moieties to achieve a pharmacologically active CD8 composition. In contrast, Applicants' invention does not employ CD8 linked to another moiety. Thus, as further elaborated in Dr Staerz's 3rd Declaration, the use of a vector as presently claimed to specifically inhibit T cells is not taught or suggested in any of the Tykocinski patents.

Second, the Tykocinski patents fail to teach use of an expression vector encoding CD8 with a transmembrane domain to effect surface expression of CD8 on a cell. Rather, the CD8:ligand constructs of the Tykocinski patents rely on their ligand portions to effect external coating. As noted above, the CD8 compositions are described as having "a CD8 peptide associated with one or more secondary ligands *that serve to direct CD8's inhibitory activity to specific target cells*." See, Tykocinski '828, column 2, lines 25-28; Tykocinski '056, column 2, lines 25-28; and Tykocinski '687, column 2, lines 27-30 (emphasis added). The specifications also provide that "[a] broad array of CD8:ligand combinations can be used, *each of which permits the targeting of CD8's modulatory activity to a specific subset of cells*." See, Tykocinski '828, column 2, lines 34036; Tykocinski '056, column 2, lines 34-36; and Tykocinski '687, column 2, lines 36-39 (emphasis added). From these statements, it is clear that the ligand portion of the constructs is required to target and bind the CD8 to specific cells. As explained at length in Dr. Staerz's 3rd Declaration, the secondary ligand of Tykocinski is responsible for binding CD8 to the target cell surface, rather than via a transmembrane domain of CD8 itself.

The Tykocinski patents further describe the linkage of their CD8 and secondary peptide ligand conjugates to portions of other transmembrane proteins. See, e.g., Tykocinski '828, columns 7, lines 19-37; Tykocinski '056, column 7, lines 18-36; and Tykocinski '687, column 7, lines 32-51. In describing the production of such constructs, the specifications provide "[c]oding sequences can be genetically engineered to create membrane-binding forms by linking, or retaining the linkage of, the coding sequences of *CD8 and secondary peptide ligands* to: 1) coding sequences for hydrophobic extension peptides of transmembrane proteins; or 2) coding sequences that direct glycoinositolphospholipid modification of peptides inside cells." Tykocinski '828, column 7, lines 26-33; Tykocinski '056, column 7, lines 25-32; and Tykocinski '687, column 7, lines 40-46 (emphasis added). As discussed in more detail in Dr Staerz's 3rd Declaration, these membrane-binding modifications necessarily occur in the "secondary peptide ligand" portions. The phrase "*CD8 and secondary peptide ligands*" establishes that the modifications apply to the linked constructs, not to CD8 alone, and the requirement for the secondary ligand to direct cell-specificity indicates membrane binding via the ligand portion. In confirmation of this teaching, the only specific example of a membrane binding CD8 construct provided by the Tykocinski patents is one that binds exclusively via its secondary ligand, namely a glycoinositolphospholipid-modified protein that is covalently linked to CD8. See, e.g., Tykocinski '828, column 7, lines 33-37; Tykocinski '056, column 7, lines 32-36; and Tykocinski '687, column 7, lines 46-51. In contrast, the present invention does not employ any secondary ligand for targeting, binding or linking other transmembrane proteins

In sum, the Tykocinski patents fail to teach the use of CD8 alpha alone to inhibit T cells, as they instead teach only the use of CD8 in association with a secondary ligand to bring about pharmacological effects. Further, the Tykocinski patents teach only the use of linked, membrane-binding ligands, not naturally associated with CD8, that target CD8's activity to specific cells. For at least either of these two reasons, Applicants respectfully request withdrawal of the anticipation rejections based on the Tykocinski patents.

**Rejections under 35 U.S.C. §103(a)**

Finally, the Office rejected claims 33-36, 37 and 39 under 35 U.S.C. §103(a) as allegedly obvious in view of any one of the Tykocinski patents in combination with Donahue, *et al.* (1997) Proc. Natl. Acad. Sci., USA, 94(9): 4664-68. Action at pages 14-15.

As Applicants have canceled claims 33-36, 37 and 39, however, Applicants respectfully submit that these rejections are rendered moot. Nonetheless, Applicants again note that the cancellation in no way indicates acquiescence to the Office's contentions regarding alleged obviousness of the claimed inventions.

## CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and respectfully request notice of the same at the Examiner's convenience. Should there by any remaining issues the Examiner is welcome to contact Applicants' representatives by telephone at (415) 781-1989.

Respectfully submitted,
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Dated: 11/21/07

By: _____
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